Remarks

Claims 1-10, 12, 15, 16, and 20-22 are pending. Claims 1, 2 and 4-7 have been amended as discussed below to clarify the claims as suggested by the examiner.

Rejection Under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 1-10, 12, 15, 16, and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The Legal Standard

35 U.S.C. §112 requires that the specification be enabling to a person skilled in the art. *See Rengo Co. Ltd. v. Molins Mach. Col.*, 657 F.2d 535, 549 (3d Cir. 1980) (every description will rely to some extent on the reader's knowledge of the terms, concepts, and depictions it embodies). The person skilled in the art is presumed to know all the art which is generally and reasonably available and has the knowledge of where to search out information. *In re Howarth*, 654 F.2d 103, 106 (CCPA 1981). The sufficiency of the specification on how to make and use the invention must be accepted unless the Patent Office provides adequate reason to doubt the accuracy of the disclosure. If the Patent Office doubts the sufficiency, then the burden shifts to the applicant to demonstrate the enablement of the disclosure by suitable evidence. Additional evidence, such as additional exemplary data and literature support, is available to substantiate any assertions that the enablement is in fact commensurate with the scope of protection sought and to respond to any demands based thereon for proof. *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Ex parte Ohukowicz*, 27 USPQ2d 1063, 1066-67 (Bd. Pat. App. & Int'f 1992).

With regard to post-filing art, the CAFC stated in In re Brana, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed." An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at the time of filing, is admissible (In re Hogan, 194 USPQ 527 (CCPA 1977)). In the latter case, as in this case, any evidence, developed at any time, may be submitted for consideration.

The test under 37 C.F.R. §112 is clear - the specification must be enabling to those skilled in the art **at the time the application is filed,** without undue experimentation. The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* supra. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable determination of how to practice desired embodiment of invention claimed. *In re Rainer*, 52 CCPA 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re Colianni, supra. *Ex parte Jackson*, 217 USPQ 804 at 807 (Bd. App. 1982).

Whether undue experimentation is needed is not based upon a single factor; it is a conclusion reached by weighing many factors. These factors were summarized in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and include:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The relative skill of those in the art;

(7) The predictability or unpredictability of the art; and

(8) The breadth of the claims.

The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to each of these factors. (see M.P.E.P. § 2164.01 (a))

The Court of Appeals for the Federal Circuit (CAFC) has most recently stated that to satisfy the legal standard for enablement under § 112, first paragraph, a patent application must adequately disclose the claimed invention to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. Enzo Biochem, Inc. v Calgene, Inc., 188 F.3d 1362, 1371-1372, 52 USPQ2d 1129 (Fed. Cir. 1999); accord

Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). However, "nothing more than objective enablement is required, and therefor it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). As set forth in In re Wright, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993):

When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

See also *In re Wands*, 8 USPQ 1400 at 1406-1407 (Fed. Cir.), stating that it does not constitute undue experimentation even when screening of large numbers is required, if there is a relatively low percentage of positives. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff. *In re Wands* at 1407. Quoting from *Utter v. Hiraga*, 845F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988), "A specification may, within the meaning of 35 U.S.C. §112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses". Quoting from *in re Robins*, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970), "[R]epresentative samples are not required by the statute and are not an end in themselves".

Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements (*In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)). Furthermore, in a recent decision by the CAFC, the court ruled that in the event that the specification described and enabled various possible species and provided specific information on methods of use, description of one species would enable one of ordinary skill to practice the method pertaining to the genus. *Amgen Inc. v. Hoescht Marion Roussel, Inc.* 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003)

There is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id*

The Present Method is Enabled by the Specification and Knowledge in the Art

The level of skill in the art is high. One of skill in the art would have been enabled to practice the claimed method with only routine experimentation. Based on the specification and the examples provided, one would be able to (1) identify an individual in need of treatment; (2) obtain agents which alter the levels of LDL, HDL or lipoproteins, and (3) administer an effective amount of the agent to change the levels of LDL, HDL or lipoproteins to alter fertility and thus treat a reproductive disorder. This is not unsupported scientific speculation.

Claim 1 specifically recites that the method is to be applied to a female mammal "in need of treatment therof"; not to a fertile, normal animal capable of reproduction.

One identifies such a patient based on well known, clinical assays showing that the lipid levels are abnormal and the female is infertile. More sophisticated assays can also be conducted, if necessary.

One then administers a drug that alters lipid levels. The examples in the application establish that the lipid levels in the experimental animals are not normal and describe assays for measurement. See, for example, Table 1, page 42. These levels are altered by administration of estrogen or genetically as described in the application.

The lack of scientific evidence in normal fertile female mammals demonstrating an effect of cholesterol-lowering drugs on altering fertility is not relevant and is not within the scope of the claims. Typically one does not see altered or abnormal lipoprotein levels in females of reproductive age.

The claimed method does not violate any scientific principles or theories. There is experimental data in the patent application to support the scientific concepts behind the claims. An article by Miettinen *et al.* has been submitted as post-filing support of enablement (see *In re Brana* 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995)). The examples in the specification include knocking out SR-BI and using adenoviral-SR-BI to alter lipoprotein, HDL, LDL, or cholesterol levels. Probucol has been shown to change the liproprotein levels and restore fertility in SR-BI knockout mice. Miettenin et al.

The role of SR-BI in fertility is clearly established by the examples in the application. The role of SR-BI in cholesteryl transport was known (see, page 10, lines 19-21). The alterations in lipoprotein and cholesterol levels in the SR-BI deficient animals is established (see Table 1, as noted above). The example provided by applicant in the post-filing application uses PROBUCOL, a well known cholesterol lowering drug, which confirms that one can normalize the lipoprotein and cholesterol levels in these animals and restore fertility. Other cholesterol lowering drugs are also available. One skilled in the art would have no trouble obtaining drugs that alter lipid levels using standard pharmaceutical texts. These are then administered at a recommended dosage and the effect on the lipid levels measured.

No undue experimentation would be required for any of these steps.

One of skill in the art would understand from the specification, which compounds to use, derive appropriate doses with minimal routine experimentation to practice the claimed method and alter fertility or treat a reproductive disorder.

Rejection Under 35 U.S.C. § 112, first paragraph (Written Description)

Claims 1-10, 12, 15, 16, and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Legal Standard

The general principle of the written description requirement for a claimed genus may be satisfied through (1) sufficient description of ***a representative number of species*** by actual reduction to practice, (2) reduction to drawings of a general structure, or (3) disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (4) describing functional characteristics coupled with a known or disclosed correlation between function and structure, or (5) a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus. *Reagents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

There is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. (MPEP at § 2164.02, citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." Id.

Although it has been argued that all candidates of a genus must be described in detail (*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997)), the Court found in Amgen that "the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, [and] renders Eli Lilly listless in this case." (*Amgen v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc*

314 F.3d 1313). In this instance, the court found that one or two species are predictive of other species in a genus. This decision has been extended to rule that adequate description of one species can satisfy the written description for the corresponding genus of compounds.

The Application Satisfies The Written Description Requirement

The first basis for the rejection is the allegation that the specification only describes a small number of specific compounds which act via SR-BI including estrogen, see example 3; adenoviral vector encoding SR-BI, see example 5; and anti-SR-BI antibody, see example 8.

This in itself seems to provide broad support for a genus claim, since it shows actual reduction to practice with three widely disparate types of compounds: a small inorganic molecule, a nucleotide molecule in a vector, and an antibody. Moreover, **all** of these compounds alter fertility by altering lipoprotein, LDL, HDL or cholesterol levels.

However, the requirement for a written description **is not** a requirement that applicants reduce to practice **all** of the species that may fall within the claimed genus. In this regard, in addition to the three examples showing actual reduction to practice, the examiner's attention is drawn to the extensive list of molecules beginning at page 11, under the section entitled "I. Inhibitors of SR-BI transport of cholesterol." and page 12, under the section entitled "II. Methods of Regulation of SR-BI cholesterol transport to alter steroidogenesis", with sub-sections for nucleotide molecules, and other molecules which alter SR-BI binding or expression (page 14) as well as the actual assays for modified LDL uptake, binding and degradation (page 15), Northern blot for expression in tissues (page 16 and pages 17-18), HDL binding (pages 16-17),

methods for screening of libraries for small organic molecules (pages 18-19), methods for designing drugs (pages 19-20), methods for obtaining nucleic acid regulators (pages 20-23), SR-BI receptor fragments (pages 24-25). Together, this description clearly conveys to those skilled in the art that, in addition to the classes of compounds actually used to show reduction to practice, a number of other molecules were known and could be screened for utility in the claimed method.

As relevantly, numerous drugs are known which can be used to normalize lipid and cholesterol levels. PROBUCOL, demonstrated by applicants to be effective in the claimed method, has been available for many years to treat atherosclerosis.

The link between fertility and cholesterol levels has now been established. Support is found in the specification on page 7, lines 21-22; page 13, lines 14-15; page 49, lines 16-20; page 49, lines 21-24 and Example 7. The Examiner agrees that Miettinen et al. supports this fact.

The claims are directed to a method for altering fertility or treating a reproductive disorder by administering a compound altering lipoprotein, LDL, HDL or cholesterol levels. This clearly indicates that only reproductive disorders that are lipid and/or cholesterol-dependent will be affected by the present method. A method to treat a reproductive disorder that is unresponsive to lipid and/orcholesterol levels by administering a compound which does not normalize lipoprotein, LDL, HDL or cholesterol levels is therefore not encompassed by the scope of these claims.

The claim limitation also reads "in an amount effective to alter fertility or treat a reproductive disorder" the dose required is an "effective amount to alter fertility or treat a reproductive disorder". The duration of treatment and thus the endpoint is similarly defined as a duration "to alter fertility or treat a reproductive disorder". The dosages and durations of treatment will vary depending on the compound to be used which can be easily titrated and determined to derive the proper values. This is common practice in the pharmaceutical arts and does not constitute undue experimentation thus satisfying the enablement requirement as well as the written description requirement of 35 U.S.C. §112, first paragraph.

The target tissues for treatment with compounds that modulate SR-BI expression are described at several places in the specification. These consist of steroidogenic tissues such as adrenals, ovaries, testes, as well as liver and fat and are described in the specification on page 12, lines 16-23, page 14, lines 27-30, page 17, lines 15-30. While these tissues are the highest expressors of SR-BI and the targets of most relevance, systemic modulation of SR-BI expression (in this example by knocking out SR-BI) demonstrates that fertility can still be altered. The use of estrogen or adenoviral - SRBI receptor in the examples has shown that methods exist to target changes in SR-BI expression to specific tissues. These compounds give representative examples of the genus and demonstrate that one of skill in the art at the time of filing would have been enabled to produce tissue-specific modulation of SR-BI to alter fertility. As clarified in the recent Amgen decision discussed *supra*, it is not necessary to list every example that may become available after the filing date to accomplish a claimed method.

The Applicants have clearly described how altering SR-BI levels in these tissues and changing serum cholesterol levels is sufficient to alter fertility or treat lipid and/or cholesterol-related reproductive disorders in a mammal. A sufficient number of examples is described and reduced to practice to satisfy the written description and enablement requirements as defined in *Amgen v TKT*. The legal standard for written description is met.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-10, 12, 15, 16, and 20-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

"Examiners are encouraged to suggest claim language to applicants to improve the clarity orprecision of the language used, but should not reject claims or insist on their own preferences in other modes of expression selected by applicants satisfy the statutory requirement." (MPEP 2173.02) Furthermore, "[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one posessing the ordinary skill in the pertinent art at the time the invention was made" (MPEP 2173.02)

The current claims are not incomplete. As is has been discussed above, the claim limitations read "in an amount effective to alter fertility or treat a reproductive disorder" and the

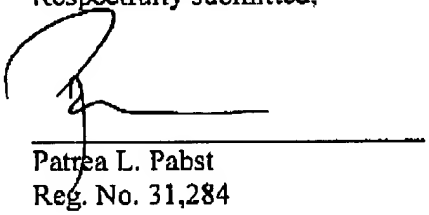
dose required is an "effective amount to alter fertility or treat a reproductive disorder". The duration of treatment and thus the endpoint are similarly defined: "to alter fertility or treat a reproductive disorder".

Solely to facilitate prosecution, the claims have been amended to recite that the dosage is effective to enhance or restore fertility.

Claims 4-7 have been amended to provide antecedant basis as the Examiner has suggested.

Allowance of claims 1-10, 12, 15, 16, and 19-22 is respectfully solicited.

Respectfully submitted,



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AMENDMENT AND RESPONSE TO OFFICE ACTION

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, May 6, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Patrea Pabst

Date: May 6, 2003